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(54) Title: ASYMMETRIC SYNTHESIS AND CATALYSIS WITH CHIRAL HETEROCYCLIC COMPOUNDS

(57) Abstract

This invention relates to chiral heterocyclic compounds useful for asymmetric synthesis and catalysis. More particularly, the invention relates to chiral heterocyclic phosphine, sulfur, and nitrogen compounds for asymmetric synthesis and catalysis in the production of enantiomerically pure products.

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Description

ASYMMETRIC SYNTHESIS AND CATALYSIS WITH CHIRAL HETEROCYCLIC COMPOUNDS

This application claims the benefit of provisional application no. 60/035,187, filed January 13, 1997 and provisional application no. 60/046,117, filed May 9, 1997.

Technical Field

This invention relates to chiral heterocyclic compounds useful for asymmetric synthesis and catalysis. More particularly, the invention relates to chiral heterocyclic phosphine, sulfur, and nitrogen compounds for asymmetric synthesis and catalysis in the production of enantiomerically pure products.

Background Art

The biological activities of many pharmaceuticals, fragrances, food additives and agrochemicals are often associated with their absolute molecular configuration. While one enantiomer gives a desired biological function through interactions with natural binding sites, another enantiomer usually does not have the same function and sometimes has deleterious side effects. A growing demand in pharmaceutical industries is to market a chiral drug in enantiomerically pure form.

To meet this challenge, chemists have explored many approaches for acquiring enantiomerically pure compounds ranging from optical resolution and structural modification of naturally occurring chiral substances to asymmetric catalysis using synthetic chiral catalysts and enzymes. Among these methods, asymmetric catalysis is often the most efficient because a small amount of a chiral catalyst can be used to

produce a large quantity of a chiral target molecule. During the last two decades, great effort has been devoted to discovering new asymmetric catalysts and more than a half-dozen commercial industrial processes have used asymmetric catalysis as the key step in the production of enantiomerically pure compounds.

The majority of current asymmetric catalytic processes relies on transition metal catalysts bearing chiral ligands. Asymmetric phosphine ligands have played a significant role in the development of transition metal catalyzed asymmetric reactions. While certain metal catalyzed phosphine chiral ligands have shown acceptable enantioselectivities in numerous reactions, there are a variety of reaction in which only modest enantioselectivity has been achieved with these ligands. The use of enzymes as asymmetric catalysts is limited because very few pure enzymes have been found to facilitate highly enantioselective catalytic reactions.

Given the limitations with transition metal catalysts and enzymes, the use of organic catalysts for asymmetric synthesis has attracted increasing attention. Compared with transition metal catalysts, there are several advantages of using pure organic catalysts: recovery of organic catalysts generally is easy since the catalysts are covalently bound and relatively stable; no contamination of toxic heavy metals exists during the reaction; and pure organic catalysts, as compared to metal catalysts, are environmentally benign.

Several organic asymmetric catalysts have been discovered and used in industrial applications. For example, chiral phosphines are known to catalyze a number of organic reactions. Vedejs et al., in the *Journal of Organic Chemistry ("J. Org. Chem.")*, Vol. 61, 8368 (1996), demonstrated phosphine-catalyzed

enantioselective acylations of secondary alcohols. Whitesell and Felman, *J. Org. Chem.*, Vol. 42, 1663 (1977), used nitrogen-based chiral auxiliaries such as trans 2,5-dimethylpyrrolidine for organic synthesis.

This invention discloses several new chiral heterocyclic compounds for asymmetric synthesis and catalysis. These compounds contain rigid ring structures useful for restricting conformational flexibility of the compounds, thus enhancing chiral recognition. The invention provides chiral heterocyclic compounds which contain phosphorous, nitrogen, and sulfur atoms within the ring structure. The chiral heterocyclic compounds disclosed in the invention allow for new catalytic asymmetric processes, including reactions proceeding by a variety of methods described herein. In such a manner, the invention provides an efficient and economical method with which to synthesize chiral drugs and agrochemicals.

Disclosure of the Invention

It is an object of the invention to provide chiral heterocyclic compounds for asymmetric synthesis and catalysis.

It is also an object of the invention to provide chiral heterocyclic phosphine, sulfur, and nitrogen compounds for asymmetric synthesis and catalysis in the production of enantiomerically pure products.

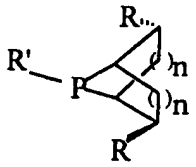
It is also an object of the invention to provide chiral heterocyclic phosphine, sulfur, and nitrogen compounds for asymmetric synthesis and catalysis in organic reactions such as [3+2] cycloaddition, nucleophilic gamma addition, Baylis-Hillman, acyl transfer, aziridation of aldehydes, epoxidation, thioether-mediation, alkylation,

deprotonation, and other commonly known asymmetric carbon-carbon bond formations.

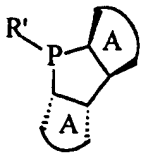
It is also an object of the invention to provide a method of making chiral heterocyclic phosphine, sulfur, and nitrogen compounds for asymmetric synthesis and catalysis.

It is also an object of the invention to provide an efficient and economical method with which to synthesize chiral drugs and agrochemicals.

In accordance with the invention, there is thus provided a chiral heterocyclic phosphine compound selected from each enantiomer of the formula **I** or **II**



I

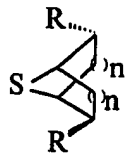


II

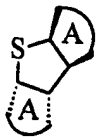
wherein n is 1 or 2; R is selected from alkyl having 1-8 carbon atoms, aryl, and substituted aryl; R' is selected from hydrogen, alkyl having 1-8 carbon atoms, aryl, and substituted aryl; and A is selected from a carbocyclic or heterocyclic, aromatic, saturated or partially saturated, mono- or bicyclic ring, which can be further substituted with one or more alkyl or aryl groups, and can comprise one or more additional chiral centers. In one embodiment of the invention, a chiral heterocyclic phosphine compound is provided as an asymmetric catalyst or a component of an asymmetric catalyst in organic reactions selected from [3+2] cycloaddition,

nucleophilic gamma addition, Baylis-Hillman, acyl transfer, and other commonly known asymmetric carbon-carbon bond formations.

In accordance with another object of the invention, there is provided a chiral heterocyclic sulfur compound selected from each enantiomer of the formula **III** or **IV**



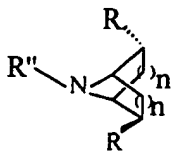
III



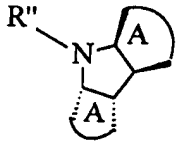
IV

wherein n is 1 or 2; R is selected from alkyl having 1-8 carbon atoms, aryl, and substituted aryl; and A is selected from a carbocyclic or heterocyclic, aromatic, saturated or partially saturated, mono- or bicyclic ring, which can be further substituted with one or more alkyl or aryl groups, and can comprise one or more additional chiral centers. In one embodiment of the invention, a chiral heterocyclic sulfur compound is provided as an asymmetric catalyst or a component of an asymmetric catalyst in organic reactions selected from aziridation of aldehydes, epoxidation, thioether- mediation, and other commonly known asymmetric carbon-carbon bond formations.

In accordance with another object of the invention, there is provided a chiral heterocyclic nitrogen compound selected from each enantiomer of the formula **V** or

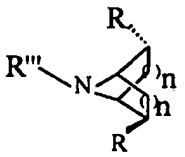


V

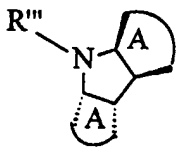


VI

VI wherein n is 1 or 2; R is selected from alkyl having 1-8 carbon atoms, aryl, and substituted aryl; A is selected from a carbocyclic or heterocyclic, aromatic, saturated or partially saturated, mono- or bicyclic ring, which can be further substituted with one or more alkyl or aryl groups, and can comprise one or more additional chiral centers; R″ is selected from hydrogen, alkyl having 1-8 carbon atoms, aryl, substituted aryl, and a group of the formula VII or VIII



VII



VIII

wherein the chiral nitrogen heterocycle in the group is identical to the other chiral nitrogen heterocycle in formula V or VI; and R′′′ is a diradical selected from alkyl diradicals having 1-8 carbon atoms, aryl diradicals, or substituted aryl diradicals. In one embodiment of the invention, a chiral heterocyclic nitrogen compound is provided as an asymmetric catalyst, a component of an asymmetric catalyst, or a chiral auxiliary in organic reactions selected from Baylis-Hillman, acyl transfer, alkylation, deprotonation, and other commonly known asymmetric carbon-carbon bond formations.

Detailed Description of the Invention

This invention pertains to a chiral heterocyclic phosphine, sulfur, or nitrogen compound for asymmetric synthesis and catalysis in the production of enantiomerically pure products.

A suitable aryl of the invention includes phenyl, furan, thiophene, pyridine, pyrole, napthyl and similar aromatic rings. Substituted aryl refers to an aryl substituted with one or more alkyl groups having 1-8 carbon atoms, alkoxy having 1-8 carbon atoms, alkylcarbonyl having 1-8 carbon atoms, carboxy, alkoxycarbonyl having 2-8 carbon atoms, halo (Cl, Br, F or I) amino, alkylamino or dialkylamino.

A suitable carbocyclic or heterocyclic, aromatic, saturated or partially saturated, mono- or bicyclic ring, which can be further substituted with one or more alkyl or aryl groups, and can comprise one or more additional chiral centers for use herein includes but is not limited to one derived from the parent compound furan, thiophene, pyrrole, tetrahydrofuran, tetrahydrothiopene, pyrrolidine, arsole or phosphole; or from the parent compound bipyridine, carbazole, benzofuran, indole, benzpyrazole, benzopyran, benzopyronone or benzodiazine.

Alkyls having 1-8 carbon atoms include straight or branched chain alkyls and cycloalkyls having 3 to 8 carbon atoms. Representative examples are methyl, ethyl, propyl, isopropyl, butyl, tertiary butyl, pentyl, cyclopentyl, hexyl cyclohexyl and the like. The alkyl group can be substituted with phenyl, substituted phenyl or alkoxy, carboxy, alkyoxycarbonyl, halo, amino, or alkyl amino or dialkylamino as defined above. Those skilled in the chemical art will recognize a wide variety of equivalent substituents.

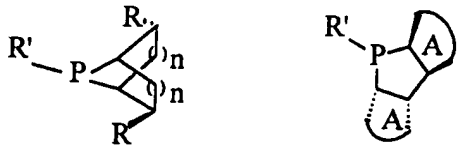
A diradical is selected from alkyl diradicals having 1-8 carbon atoms, aryl diradicals, or substituted aryl diradicals. A suitable diradical includes but is not limited to $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-C_6H_4-$, or ortho-substituted-C_6H_4-, and the like.

The invention encompasses a variety of asymmetric reactions utilizing catalysts of the invention, such as [3+2] cycloaddition, nucleophilic gamma addition, Baylis-Hillman, acyl transfer, aziridation of aldehydes, epoxidation, thioether-mediation, alkylation, deprotonation, and other commonly known asymmetric carbon-carbon bond formations. The catalyst of the invention provides efficient and practical methods for producing chiral drugs for antihypertensive, antihistamine, cardiovascular and central nervous system therapies. The chiral heterocyclic compounds of the invention are also important in the production of chiral agrochemicals.

CHIRAL, HETEROCYCLIC PHOSPHINE, SULFUR, AND NITROGEN COMPOUNDS

The invention provides chiral heterocyclic compounds containing phosphorous, sulfur, and nitrogen atoms. Chiral heterocyclic phosphine compounds, e.g., phosphabicyclo[2.2.1]heptanes **I** and phosphacycle **II** are shown in Figure 1.

Fig. 1



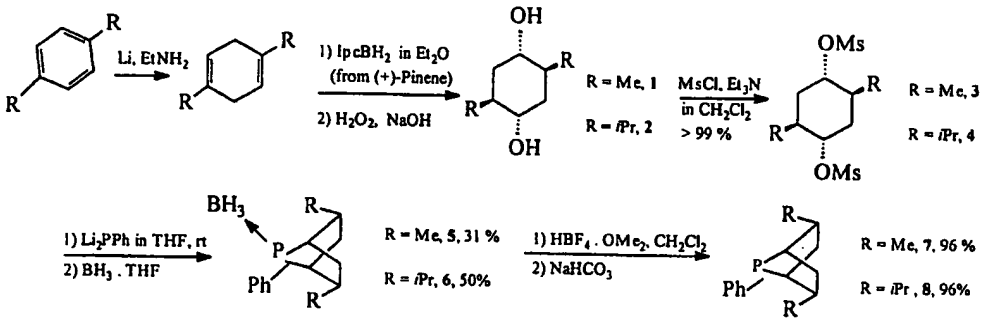
I **II**

Both **I** and **II** contain rigid fused bicyclo structures which restrict conformational flexibility in the chiral system, leading to high enantioselectivity for a variety of asymmetric reactions described above.

The synthesis of chiral phosphabicyclo[2.2.1]heptanes depends on the availability of enantiomerically pure cyclic 1,4-diols (Scheme 1). Halterman et al.,

Organometallics, Vol. 10, 3449 (1991) and Vollhardt, *Journal of the American Chemical Society* ("*J. Am. Chem. Soc.*"), Vol. 109, 8105 (1987) have previously prepared chiral cyclopentadiene derivatives from chiral diols. Halterman has synthesized chiral diols **1** and **2** from the inexpensive starting materials p-xylene and p-diisopropylbenzene, respectively.

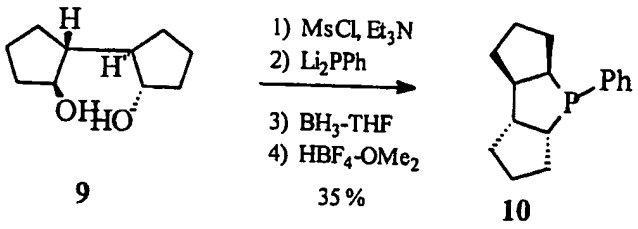
The synthesis employed Birch reduction, followed by asymmetric hydroboration and recrystallization to 100% enantiomeric excess ("ee"). Conversion of the optically



Scheme I

pure diols to the corresponding mesylates proceeds cleanly. Nucleophilic substitution by Li_2PPh on the chiral dimesylates **3** and **4** generated the corresponding bicyclic phosphines, which were trapped by BH_3-THF to form the air-stable boron-protected monophosphines **5** and **6**, respectively. Deprotection with a strong acid produces the desired products [**7**, (1R, 2S, 4R, 5S)-(+)-2, 5-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane; **8**, (1R, 2R, 4R, 5R)-(+)-2, 5-diisopropyl-7-phenyl-7-phosphabicyclo-[2.2.1]heptane] in high yields.

The chiral phosphacycle **10** was synthesized by the route show in Scheme 2.

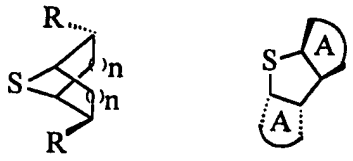


9 **10**

Scheme 2

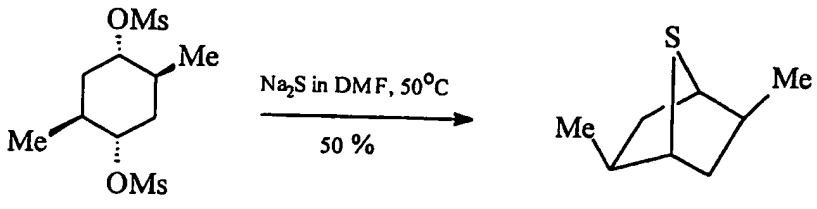
Chiral heterocyclic sulfur compounds, thiobicyclo[2.2.1]heptanes, **III**, and thiocycle **IV**, are shown in Figure 2.

Fig. 2



III **IV**

Thiobicyclo[2,2,1]heptanes (e.g., **III**) can be made by nucleophilic addition of Na_2S to the chiral dimesylates (Scheme 3).



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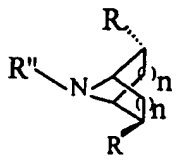
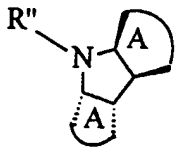
Scheme 3

Chiral heterocyclic nitrogen compounds, e.g., azabicyclo[2,2,1]heptanes **V**, and azacyclo **VI** were made by a slightly different route (Scheme 4).

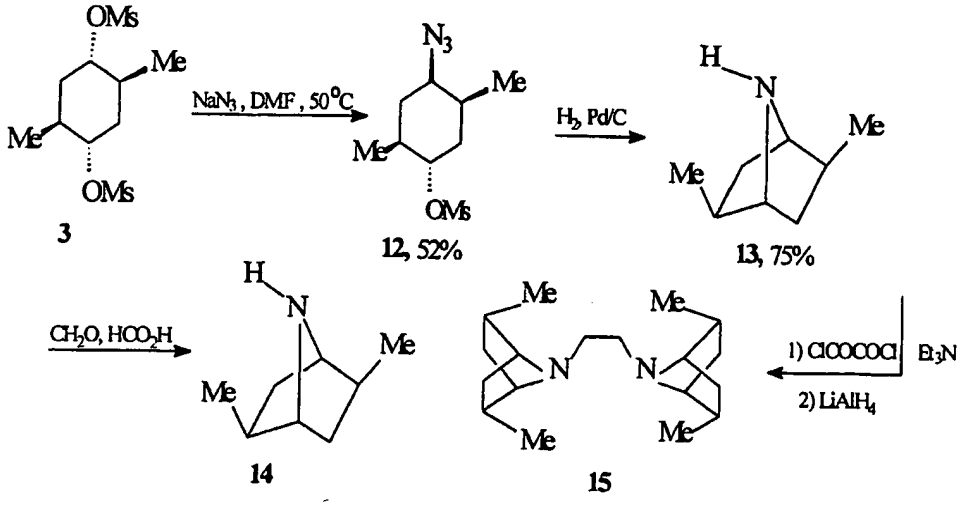


V



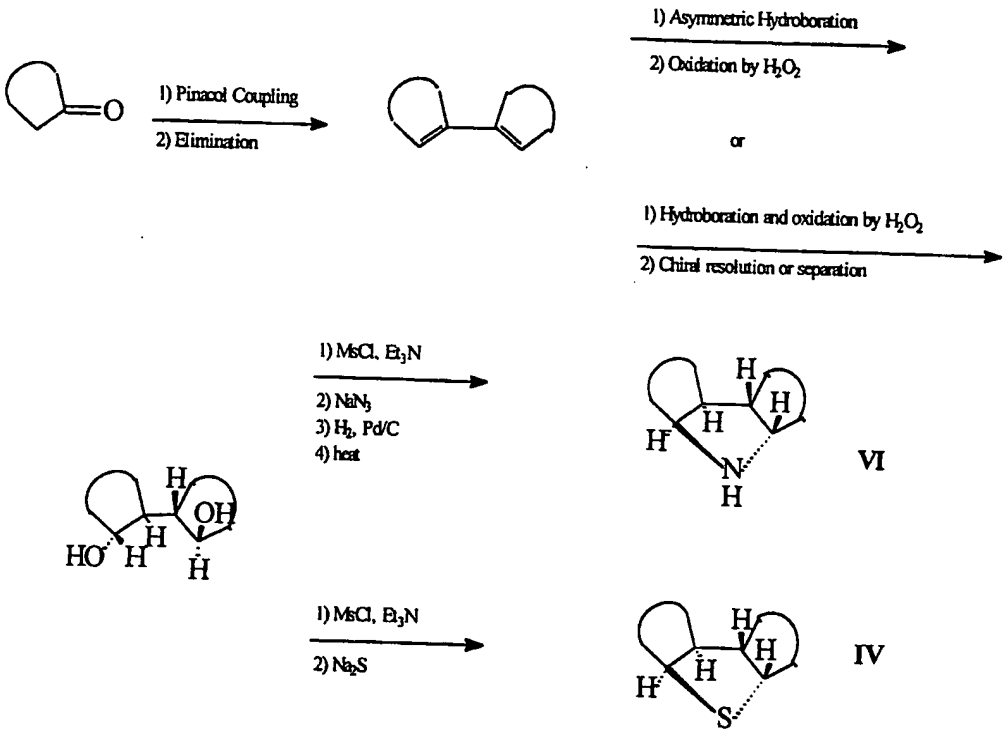
VI

Nucleophilic addition of azide to dimesylate **3** forms intermediate **12**. Reduction of **12** with H_2 to an amine and intramolecular closure of the amine on to the mesylate occurs smoothly in the same operation gives the desired product **13**. Further straightforward reactions lead to the other desired chiral nitrogen containing compounds **14** and **15**.



Scheme 4

The sulfur and nitrogen chiral heterocyclic compounds of the general formula IV and VI were synthesized according to the method shown in Scheme 5.



Scheme 5

ASYMMETRIC SYNTHESIS AND CATALYSIS USING CHIRAL HETEROCYLIC COMPOUNDS

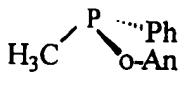
The invention is illustrated by using the chiral heterocyclic compounds of the invention in asymmetric synthesis and catalysis.

[3+2] CYCLOADDITIONS WITH CHIRAL HETEROCYCLIC COMPOUNDS

The identification of the prostaglandins, steroids and related natural products as important synthetic targets has stimulated the development of many diverse strategies for the synthesis of five-membered carbocycles. The efficient stereoselective synthesis of highly functionalized cyclopentane rings remains an

important challenge in organic chemistry. Among the reported methods for the synthesis of five-membered ring carbocycles, [3+2] cycloadditions have the advantage of simultaneously forming multiple bonds, although issues of chemo-, regio-, diastereo- and enantioselectivity must be resolved if such a process is to achieve useful generality. Transition metal-catalyzed, anionic, cationic, and free radical mediated [3+2] cycloadditions have previously been investigated in the formation of five-member carbocycles. However, none of these methods produce the regioselectivity, enantioselectivity, and scope of application for the synthesis of cyclohexane derivatives.

Asymmetric [3+2] cycloadditions were conducted using several known chiral phosphine catalysts (**16-18**) to provide comparison points with [3+2] cycloadditions conducted with the chiral heterocyclic phosphine compound of the invention.



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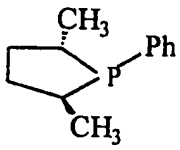

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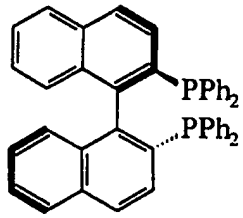

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The asymmetric reactions were done by mixing ethyl 2,3-butadienoate and ethyl acrylate in benzene with 10 mol % of phosphine at room temperature. Table 1 lists the results with different chiral heterocyclic phosphine compounds.

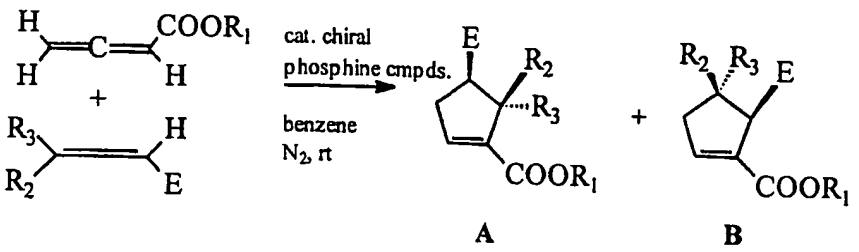


Table 1. Phosphine-Catalyzed Asymmetric (3+2) Cycloaddition[a]

Entry	Phospine	E	R_1	R_2	R_3	solvent	T(°C)	Yield (%)	A:Bb	%ee of A[b]	Config.[c]
1	7	COOEt	Et	H	H	benzene	rt	66	95:5	81	(-)R
2	8	COOEt	Et	H	H	benzene	rt	76	97:3	81	(-)R
3	16	COOEt	Et	H	H	benzene	rt	80	80:20	56	(+)S
4	17	COOEt	Et	H	H	benzene	rt	83	72:29	6	(+)S
5	18	COOEt	Et	H	H	benzene	rt	33	73:27	12	(-)R
6	7	COO^{t}Bu	Et	H	H	benzene	rt	46	100:0	86	(-)R
7	7	COO^{t}Bu	Et	H	H	benzene	rt	69	95:5	89	(-)R
8	7	COO^{t}Bu	Et	H	H	toluene	0	42	97:3	93	(-)R
9	8	COOM	Et	H	H	benzene	rt	87	96:4	79	(-)R
10	8	COO^{t}Bu	Et	H	H	benzene	rt	92	100:0	88	(-)R
11	8	COO^{t}Bu	Et	H	H	toluene	0	88	100:0	93	(-)R
12	8	COO^{t}Bu	Et	H	H	benzene	rt	75	95:5	88	(-)R
13	7	COOEt	tBu	H	H	benzene	rt	13	97:3	89	(-)R
14	8	COOEt	tBu	H	H	benzene	rt	84	94:6	69	(-)R
15	8	COOEt	Et	COOEt	H	benzene	rt	49	———	79	(+)
16	8	COOEt	Et	H	COOEt	benzene	rt	84	———	36	(-)

a. The reaction was carried out under N_2 using a chiral phosphine (10 mol %), 2,3-butadienoate (100 mol %) and an electron deficient olefins (100 mol %). b. A:B and % ee were measured by GC using β and γ-DEX columns. The absolute configuration was determined by comparing the optical rotation with the literature value.

Phosphabicyclo[2.2.1]heptanes **7-8** are more effective both in terms of regioselectivity (**A:B** ratio) and enantioselectivity (% ee of **A**) than known chiral phosphines **16-18**. The absolute configuration of product **A** was assigned by correlation with (1R, 3R)-dihydroxymethyl-3-cyclopentane. In particular, the enantioselectivity with 7 (81% ee, R) is much higher than with 17 (6% ee, S), which illustrates the consequences of using a rigid bicyclic [2.2.1] structure rather than the conformationally more flexible five-membered ring phosphine.

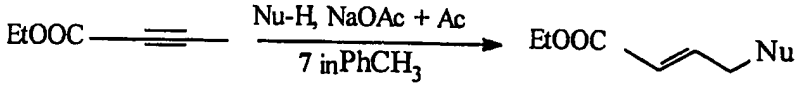
Changing the size of ester group in the electron-deficient olefin alters the enantioselectivity. With phosphine 7, the enantioselectivity increases as the size of ester increases (entry 1, Et, 81% ee; entry 6, ^{i}Bu, 86% ee; entry 7, ^{t}Bu, 89% ee). A similar trend was observed with phosphine **8** (entries 2, 9-10, and 12). Upon cooling the reaction to 0 ^{0}C in toluene, up to 93 % ee of **A** was obtained with phosphines **7-8** with excellent regioselectivity (entries 8 and 11). Increasing the size of the ester moiety in the 2,3-butadienoates, however, has different effects on the product ee with phosphine 7 (entry 1, Et, 81% ee; entry 13, ^{t}Bu, 89% ee) or **8** (entry 2 , Et, 81% ee; entry 14, ^{t}Bu, 69% ee). A second major difference between catalysis by 7or **8** is in the yield of products. The conversion to the desired products with **8** is generally higher than with 7 (e.g., entries 6-8 vs entries 9-12). With diethyl maleate (entry 15) and diethyl fumarate (entry 16) as substrates, single *cis*- and *trans*-products were obtained with **8**, respectively. While the % ee of the *cis*-product (entry 15, 79% ee) is slightly lower than the result with ethyl acrylate (entry 2, 81% ee), the *trans*-product has much lower optical purity (entry 16, 36% ee). As indicated by the Table 1, a [3+2] cycloaddition between 2,3-butadienoates and electron deficient olefins catalyzed by the chiral heterocyclic compounds of the invention provides cyclopentene products with excellent regioselectivity and enantioselectivity.

ASYMMETRIC NUCLEOPHILIC GAMMA ADDITION

The success of chiral heterocyclic phosphine catalyzed [3+2] cycloadditions between 2,3-butadienoates and electron-deficient olefins prompted further examination of other chiral heterocyclic phosphine catalyzed reactions. One such reaction, discovered by Trost, *J. Am. Chem. Soc.*, Vol. 116, 3167 (1994), is the

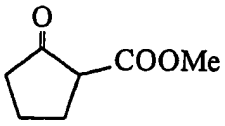
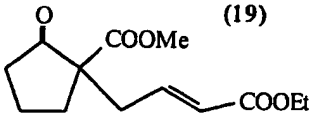
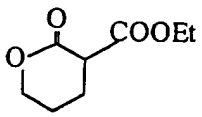
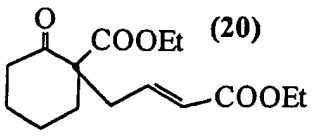
phosphine catalyzed "umpolung" C-C bond formation at the γ-position of 2-butynoates with malonate-type nucleophiles (Scheme 6). In this phosphine catalyzed "umpolung" C-C bond forming reaction, generation of electrophilic character at the γ-carbon of 2-butynoates creates a regiochemical complement to the Michael addition.

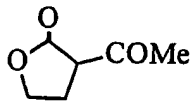
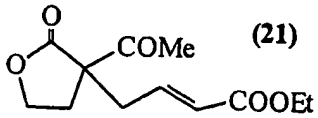
Using chiral phosphabicyclo[2.2.1]heptanes **7** and **8** as catalysts, and under conditions similar to those cited by Trost, moderate enantioselectivities (42-68% ee, entry 1-4) have been obtained between ethyl 2-butynoate and several pronucleophiles with **7** as the catalyst (Table 2).



Scheme 6

Table 2. Phosphine-Catalyzed Asymmetric γ-Addition[a]

1		80	16	76	59(-)	 **(19)**
2		50	72	57	68(-)	
3		110	50	44	51(+)	 **(20)**

4		110	18	93	43(-)		(21)

a: The reaction was carried out under N_2 with chiral phosphine 1 (30 mol%), NaOAc (50 mol%), acetic acid (50 mol%), ethyl 2-butynoate (100 mol%) and Nu-H (100 mol%). b: % ee was measured by GC with a γ-Dex column.

Under milder reaction conditions, using ethyl 2,3-butadienoate as an electrophile instead of 2-butynoate, the γ-addition reaction was conducted under various conditions by changing catalysts, additives, and substrates. Table 3 lists the results of this asymmetric reaction with several chiral phosphines (**7, 8, 10, 16-18**).

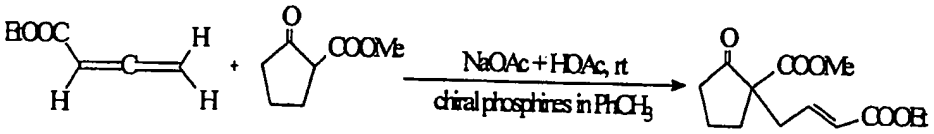


Table 3. Asymmetric γ-Addition Catalyzed by Various Chiral Phosphines[a]

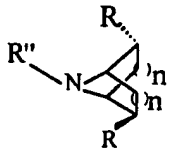
Entry	Phosphine	Time	Yield (5)	ee % [b]	rotation
1	**7**	27 h	76	74	-
2	**8**	27 h	80	69	-
3	**10**	18	71	35	+
4	**16**	4 d	58	8	-
5	**17**	5 d	66	20	+
6	**18**	>10 d	46	20	+

a: The reaction was carried out under N_2 at rt. With chiral phosphines (1-6) (10 mol%), NaOAc (50 mol%), AcOH (50 mol%), ethyl 2,3-butadienoate (100 mol%) and 2-methoxycarbonyl cyclopentanone (100 mol%). B: % ee was measured by GC with a γ-Dex column.

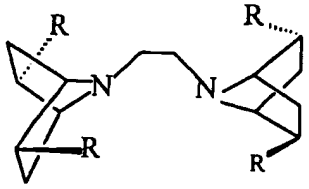
The new phosphines **7** and **8** (entries 1-2) are more selective and active catalysts than the previously reported chiral phosphines **16-18** (entries 4-6). Compared to the conformationally rigid dimethyl phosphabicyclo[2.2.1]heptane **7** (entry 1, 74% ee), the corresponding five-membered ring phosphacycle **16** gives much lower enantioselectivity (entry 4, 8% ee). This result is similar to that observed in the asymmetric cyclic phosphine catalyzed [3+2] cycloaddition described above. Phosphacycle **10** produced moderate enantioselectivity (entry 3).

Other Applications of the Invention

Many other asymmetric organic reactions can by facilitated by the chiral heterocyclic compounds of the invention. For example, the chiral heterocyclic nitrogen compound of general formula **V** or compound **15** can be used as chiral catalysts or auxiliaries for asymmetric deprotonation, enamine alkylation, cycloaddition reactions, and the Baylis-Hillman reaction. The dimer derivative of azabicyclo[2.2.1]heptane, **15**, can serve as a chiral



V



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auxiliary in an asymmetric deprotonation. The fused [2.2.1] structure in **V** makes the nitrogen lone pair more nucleophilic than other trialkyl amines such as Et_3N.

The chiral heterocyclic sulfur compounds of the invention are particularly suited for use in asymmetric epoxidation of aldehydes. Most epoxidation systems

are still not very efficient for unfunctionalized trans-olefins. Direct epoxidation of carbonyl compounds using sulfur ylides formed from **III** and **IV** provides a route for the formation of chiral trans epoxides. One target is (2R, 2S)-3-(4-methoxyphenyl) glycidate, which is a key intermediates for the synthesis of diltiazem hydrochloride, a potent blocker used for the treatment of anginina pectoris and hypertension.

Like epoxides, aziridines are important chiral building blocks in organic chemistry. Aggarwal et al., *J. Org. Chem.*, Vol. 61, 430 (1996), applied his epoxidation system for asymmetric aziridination by replacing aldehydes with imines as the substrates, with impressive selectivity results. The application of chiral heterocyclic sulfur compounds of the general formula **III** or **IV** as asymmetric catalysts should similarly provide high enantioselectivity for a variety of substrates.

EXAMPLES

Unless otherwise indicated, all reactions were carried out under nitrogen. THF and ether were freshly distilled from sodium benzophenone ketyl. Toluene and 1,4-dioxane were freshly distilled from sodium. Dichloromethane and hexane were freshly distilled from CaH_2. Column chromatography was performed using EM Silica gel 60 (230~400 mesh). ^{1}H, ^{13}C and ^{31}P NMR were recorded at 300 or 360 MHZ NMR spectrometers. Chemical shifts are reported in ppm downfield from TMS with the solvent resonance as the internal standard. Optical rotation was obtained on a Perkin-Elmer 241 polarimeter. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-EI and HR-EI. GC analysis were done using chiral capillary columns (Supelco γ-Dex 225 or β-Dex 120).

Example 1

Compounds **1-4** (shown in Scheme 1) were prepared according to literature procedure. *See, e.g.*, Halterman et al., Organometallic, Vol. 15, 3957 (1996); Halterman & Chen, *J. Am. Chem. Soc.*, Vol. 114, 2276 (1992).

Example 2

(1*R*, 2*S*, 4*R*, 5*S*)-(+)-2, 5-Dimethyl-7-phenyl-7-phosphabicyclo[2,2,1]heptane borane (5). To phenylphosphine (3.0 ml, 27.3 mmol) in THF (200 mL) was added n-BuLi (34.5 mL of a 1.6 M solution in hexane, 55 mmol) via syringe at -78 °C over 20 min. Then the orange solution was warmed up to rt and stirred for one hour at room temperature. To the resulting orange-yellow suspension was added a solution of (1*S*,2*S*,4*S*,5*S*)-2,5-dimethyl-cyclohexane-1,4-diol bis(methanesulfonate) (8.25 g, 27.5 mmol) in THF (100 mL) over 15 min. After the mixture was stirred overnight at room temperature, the pale-yellow suspension was hydrolyzed with NH_4Cl-saturated aqueous solution. The mixture was extracted with ether (2 x 50 mL), and the combined organic solution was dried over anhydrous sodium sulfate. After filtering , the solvents were removed under reduced pressure. The residue was taken into methylene chloride (100 mL) and treated with BH_3·THF (40 mL of a 1.0 M solution in THF, 40 mmol). After being stirred overnight, it was poured into NH_4Cl-saturated aqueous solution which was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic solution was dried over anhydrous Na_2SO_4. After filtration, the solvent was removed on rotavapor. The residue was subjected to chromatography on silicon gel column, eluted with hexanes/CH_2Cl_2 (4:1). The product was isolated as a white solid, soluble in $CHCl_3$, THF, ether and AcOEt. Yield: 1.95 g (31%). $[\alpha]^{25}_D$ = + 59.5° (c

1.07, $CHCl_3$).^{1}H-NMR ($CDCl_3$): δ 7.60-7.30 (m, 5 H, $C_6\underline{H}_5$), 2.60-2.40 (m, 2 H, C$\underline{H}$P(BH_3)Ph), 2.15-2.05 (m, 1 H, C$\underline{H}$), 2.04-1.80 (m, 4 H, C$\underline{H}_2$), 1.65-1.50 (m, 1 H, C$\underline{H}$), 1.32 (d, ^{3}J(HH) = 6.5 Hz, 3 H, C$\underline{H}_3$), 0. 59 (d, ^{3}J(HH) = 6.7 Hz, 3 H, C$\underline{H}_3$), 1.6-0.2 (br, B$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$): δ 131.74 (d, ^{2}J(PC) = 7.3 Hz, C_{ortho}), 130.56 (d, ^{1}J(PC) = 43.9 Hz, C_{ipso}), 129.92 (d, ^{4}J(PC) = 2.0 Hz, C_{para}), 128.44 (d, ^{3}J(PC) = 8.6 Hz, C_{meta}), 43.07 (d, ^{1}J(PC) = 30.5 Hz, $\underline{C}$HP(BH_3)Ph), 40.85 (d, ^{1}J(PC) = 31.6 Hz, $\underline{C}$HP(BH_3)Ph), 36.27 ($\underline{C}H_2$), 36.67 (d, ^{3}J(PC) = 13.5 Hz, CH_2), 35.91 (d, ^{2}J(PC) = 3.5 Hz, $\underline{C}$H), 34.65 (d, ^{2}J(PC) = 9.8 Hz, $\underline{C}$H), 20.78 ($\underline{C}H_3$) 20.53 ($\underline{C}H_3$); ^{31}P-NMR ($CDCl_3$): δ 36.3 (d, broad, ^{1}J(PB) = 58.8 Hz). MS m/z 232 (M^+, 0.42), 218 (M^+-BH_3, 100), 203 (7.41), 176 (14.60), 136 (9.81), 109 (16.67), 91 (6.59), 77 (5.51), 65 (3.71); HRMS Calcd for $C_{14}H_{22}BP$: 232.1552 (M^+); found: 232.1578; $C_{14}H_{19}P$: 218.1224 (M^+-BH_3); found: 218.1233.

Example 3

(1*R*, 2*R*, 4*R*, 5*R*)-(+)-2, 5-Diisopropyl-7-phenyl-7-phosphabicyclo[2,2,1]heptane borane (6). Using the same procedure as in the preparation of **5.** Yield: 0.33 g (50%). $[\alpha]^{25}_D$ = + 25.5° (c 1.02, $CHCl_3$).^{1}H-NMR ($CDCl_3$): δ 7.55-7.30 (m, 5 H, $C_6\underline{H}_5$), 2.85-2.70 9 (m, 2 H C$\underline{H}$P(BH_3)Ph), 2.30-2.20 (m, 1 H, C$\underline{H}$), 2.18-2.00 (m, 1 H, C$\underline{H}$), 1.95-1.65 (m, 4 H, C$\underline{H}_2$), 1.40-1.20 (m, 2 H, C$\underline{H}$), 1.03 (d, ^{3}J(PH) = 6.5 Hz, C$\underline{H}_3$), 0.87 (d, ^{3}J(PH) = 6.7 Hz, C$\underline{H}_3$), 0.85 (d, ^{3}J(PH) = 7.4 Hz, C$\underline{H}_3$), 0.53 (s, broad, 3 H, C$\underline{H}_3$), 1.5-0.2 (broad, B$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$): δC = 131.19 (d, ^{2}J(PC)= 8.3 Hz, C_{ortho}), 130.71 (d, ^{1}J(PC) = 45.2 Hz, C_{ipso}), 129.97 (d, ^{4}J(PC) = 2.5 Hz, C_{para}), 128.45 (d, ^{3}J(PC) = 9.5 Hz, C_{meta}), 50.30 (d, ^{2}J(PC) = 2.1 Hz, CH), 48.77 (d, ^{2}J(PC) = 9.7 Hz, CH), 38.27 (d, ^{1}J(PC) = 30.5 Hz, $\underline{C}$HP(BH_3)Ph), 36.81 (CH_2), 36.71 (d,

^{1}J(PC) = 31.5 Hz, CHP(BH_3)Ph), 34.73 (d, ^{3}J(PC) = 13.7 Hz, CH_2), 31.92 (CHMe$_2$), 31.12 (CHMe$_2$), 22.41 (CH_3), 21.55 (CH_3), 20.73 (CH_3), 20.10 (CH_3); ^{31}P-NMR ($CDCl_3$) δ 36.d (d, broad, ^{1}J(PB) = 51.4 Hz).

Example 4

(1*R*, 2*S*, 4*R*, 5*S*)-(+)-2, 5-Dimethyl-7-phenyl-7-phosphabicyclo[2,2,1]heptane (7)

To a solution of corresponding borane complex of the phosphine (1.0 g, 4.31 mmol) in CH_2Cl_2 (22 mL) was added tetrafluoroboric acid-dimethyl ether complex (2.63 mL, 21.6 mmol) dropwise via a syringe at -5 ^{0}C. After the addition, the reaction mixture was allowed to warm up slowly, and stirred at rt. After 20 h, ^{31}P NMR showed the reaction was over, it was diluted by CH_2Cl_2, neutralized by saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, followed by water, and then dried over Na_2SO_4. Evaporation of the solvent gave a pure phosphine product, which was confirmed by NMR. Yield: 0.9 g (96%). $[\alpha]^{25}_D$ = +92.5° (c 2.3, toluene); ^{1}H NMR ($CDCl_3$, 360 MHZ) δ 7.38~7.34 (m, 2H), 7.26~7.21 (m, 2H), 7.19~7.16 (m, 1H), 2.60~2.54 (m, 2H), 1.89~1.62 (m, 5H), 1.44~1.42 (m, 1H), 1.16 (d, J = 6.12 Hz, 3H), 0.55 (d, J = 6.95 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.68 (d, J = 29.3 Hz), 131.42 (d, J = 13.0 Hz), 127.88 (d, J = 2.35 Hz), 126.57 (s), 47.34 (d, J = 13.5 Hz), 45.26 (d, J = 10.2 Hz), 39.21 (d, J = 6.7 Hz), 39.21 (d, J = 5.3 Hz), 38.74 (d, J = 6.7 Hz), 34.69 (d, 17.2 Hz), 22.37 (d, J = 7.8 Hz), 21.52 (s); ^{31}P NMR($CDCl_3$) δ -7.29.

Example 5

(1*R*, 2*R*, 4*R*, 5*R*)-(+)-2, 5-Diisopropyl-7-phenyl-7-phosphabicyclo[2,2,1]heptane (8). Using the same procedure as in the preparation of **7**. Yield: 1.0 g (95.5%). $[\alpha]^{25}_D$

= +43.9° (c 1.2, toluene); ^{1}H NMR ($CDCl_3$, 360 MHZ) δ 7.35~7.30 (m, 2H), 7.24~7.14 (m, 3H), 2.94~2.85 (m, 2H), 1.76~1.53 (m, 5H), 1.25~1.14 (m, 2H), 1.06 (d, J = 7.77 Hz, 3H), 0.95~08.0 (m, 1H), 0.87 (dd, J = 3.77 Hz, 7.89 Hz, 6 H), 0.49 (d, J = 9.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.83 (d, J = 30.49 Hz), 130.69 (d, J = 12.2 Hz), 127.71 (d, J = 2.87 Hz), 126.45 (s), 53.38 (d, J = 6.34 Hz), 48.63 (d, J = 17.06 Hz), 41.97 (d, J = 13.43 Hz), 40.51 (d, J = 9.96 Hz), 37.60 (d, J = 11.09 Hz), 37.39 (d, J = 9.74 Hz), 33.03 (d, 6.11 Hz), 31.86 (s), 21.89 (s), 21.78 (s), 21.23 (s), 20.40 (s); ^{31}P NMR($CDCl_3$) δ -7.49.

Example 6

Enantioselective [3+2] Cycloaddition: General Procedure for Asymmetric [3+2] Cycloaddition as Shown in Table 1. *The procedure is exemplified by the reaction of ethyl 2,3-butadienoate and methyl acrylate in the presence of* **8**. Under the nitrogen, to a solution of ethyl 2,3-butadienoate (112 mg, 1.0 mmol) and methyl acrylate (0.9 ml, 10 mmol) in benzene (5 ml) was added chiral heterocyclic phospine compound **8** (1.0 ml of 0.1M solution in toluene, 0.1 mmol) dropwise via syringe at room temperature. After stirring the mixture for 3 hours, TLC showed the reaction was complete. The ratio of two regioisomers (**A:B** = 96:4) and enantiomeric excesses of the crude reaction mixture (79% ee of **A** and 0% of **B**) were measured by Capillary GC. After the reaction mixture was concentrated in *vacuo*, the residue was purified by chromatograpy on a silica gel column (hexanes/ethyl acetate, 15:1). Yield: 175 mg, 87%.

Example 7

Preparation of Compound 10 (as shown in Scheme 2)

(1*R*, 1'*R*)-Bicyclopentyl-(2*S*, 2'*S*)-diol Bis(methanesulfonate) (9). To a solution of (1*R*, 1'*R*)-bicyclopentyl-(2*S*, 2'*S*)-diol (0.8 g, 4.65 mmol) and triethylamine (1.68 mL, 12.09 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of methanesulfonyl chloride (0.76 mL, 9.92 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 30 min at 0 °C, the reaction mixture was stirred for an additional 2 h at rt, then quenched by saturated aqueous ammonium chloride solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic solution was dried over Na_2SO_4. After evaporation of the solvent, a white solid was obtained which was used directly for the next step. ^{1}H NMR ($CDCl_3$, 200 MHZ) δ 5.01(m, 2H), 3.04 (s, 6 H), 2.17 (m, 2 H), 2.15-1.65 (m, 10 H), 1.43-1.52 (m, 2 H); ^{13}C NMR δ 86.8, 48.2, 38.4, 32.8, 27.4, 22.5.

10-BH_3. To phenylphosphine (0.39 mL, 3.55 mmol) in THF (50 mL) was added n-BuLi (4.9 mL of a 1.6 M solution in hexane, 7.8 mmol) via syringe at 0 °C over 2 min. The orange solution was warmed to rt and stirred for 1 h. To the resulting orange-yellow suspension was added a solution of (1*R*, 1'*R*)-bicyclopentyl-(2*S*, 2'*S*)-diol bis(methanesulfonate) (1.16 g, 3.55 mmol) in THF (30 mL) over 3 min. After the mixture was stirred overnight at rt, the pale-yellow suspension was hydrolyzed with saturated NH_4Cl solution. The mixture was extracted with ether (2 x 50 mL), and the combined organic extract was dried over anhydrous Na_2SO_4, and evaporated. The residue was dissolved in CH_2Cl_2 (30 mL), treated with BH_3·THF (10 mL of a 1.0 M solution in THF, 10 mmol) and the mixture was stirred overnight. Work up required addition of saturated NH_4Cl solution and extraction with CH_2Cl_2 (30 mL).

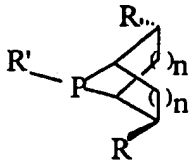
The combined organic extract was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography, eluting with hexanes/CH_2Cl_2 (3:1) affording the product as a white solid. Yield: 0.35 g (38%). ^{1}H-NMR ($CDCl_3$) δ 7.80-7.65 (m, 2 H), 7.55-7.35 (m, 3H), 3.00-2.10 (m, 4 H), 2.00-1.30 (m, 12 H), 1.30-0.20 (m, 3H); ^{13}C-NMR ($CDCl_3$)_δ 132.2 (d, ^{2}J(PC) = 8.0 Hz), 130.8 (d, ^{4}J(PC) = 2.3 Hz), 129.3 (d, ^{1}J(PC) = 45.2 Hz), 128.6 (d, ^{3}J(PC) = 9.2 Hz), 53.5 (d, ^{2}J(PC) = 5.1 Hz), 52.6 (d, ^{2}J(PC) = 6.0 Hz), 45.3 (d, ^{1}J(PC) = 35.9 Hz), 41.0 (d, ^{1}J(PC) = 37.1 Hz), 32.3 (d, ^{2}J(PC) = 5.1 Hz), 32.0 (d, ^{2}J(PC) = 6.6 Hz), 28.1 (d, ^{3}J(PC) = 5.0 Hz), 27.8 (d, ^{3}J(PC) = 4.8 Hz), 26.1 (d, ^{3}J(PC) = 6.7 Hz), 25.8 (d, ^{3}J(PC) = 6.0 Hz); ^{31}P-NMR ($CDCl_3$) δ 48.1 (q, br, ^{1}J(PB) = 53 Hz).

Preparation of Compound 10. To a solution of **10**-BH_3 (0.293 g, 1.34 mmol) in CH_2Cl_2 (8 mL) was added tetrafluoroboric acid-dimethyl ether complex (0.69 mL, 5.69 mmol) dropwise via syringe at -5 °C. After the addition, the reaction mixture was allowed to warm slowly to rt and was stirred for 20 h. When ^{31}P NMR showed the reaction was complete, the mixture was diluted with CH_2Cl_2, neutralized with saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, followed by water, and then dried over Na_2SO_4. Evaporation of the solvent gave a pure phosphine product **10**. Yield: 0.256 g (92%). ^{1}H NMR ($CDCl_3$, 360 MHZ) δ 7.46~7.42 (m, 2H), 7.35~7.26 (m, 3H), 2.93~2.77 (m, 2 H), 2.50~2.40 (m, 2 H), 2.09~2.01 (m, 1 H), 1.87~1.42 (m, 10 H), 1.28~1.19 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 139.46 (s),

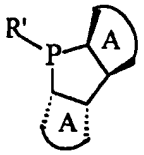
139.20 (s), 132.28 (s), 132.09 (s), 127.91 (d, J = 5.25 Hz), 127.42 (s), 54.48 (d, J = 1.99 Hz), 53.34 (s), 44.85 (d, J = 13.40 Hz), 44.13 (d, J = 6.61 Hz), 32.49 (m), 32.23 (s), 31.89 (s), 29.09 (d, J = 5.16 Hz), 26.05 (s), 25.60 (d, J = 7.88 Hz); ^{31}P NMR ($CDCl_3$) δ 16.33.

Claims

1. A chiral heterocyclic phosphine compound selected from each enantiomer of the formula **I** or **II**



I



II

wherein:

n is 1 or 2;

R is selected from alkyl having 1-8 carbon atoms, aryl, and substituted aryl;

R' is selected from hydrogen, alkyl having 1-8 carbon atoms, aryl, and substituted aryl; and

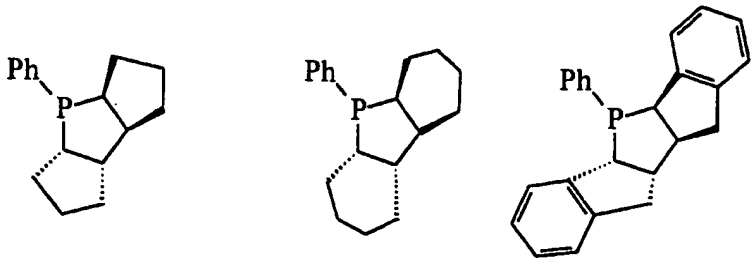
A is selected from a carbocyclic or heterocyclic, aromatic, saturated or partially saturated, mono- or bicyclic ring, which can be further substituted with one or more alkyl or aryl groups, and can comprise one or more additional chiral centers.

2. A compound according to claim 1, wherein R is methyl, ethyl, or isopropyl.

3. A compound according to claim 2, wherein R' is phenyl.

4. A compound according to claim 1 wherein the ring comprises 3 to 8 carbon or heteroatoms per ring.

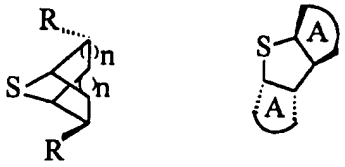
5. A compound according to claim 4 selected from



wherein Ph is phenyl.

6. A chiral heterocyclic phosphine compound according to claim 1 used as an asymmetric catalyst or as a component of an asymmetric catalyst in organic reactions selected from [3+2] cycloaddition, nucleophilic gamma addition, Baylis-Hillman, acyl transfer, and other commonly known asymmetric carbon-carbon bond formations.

7. A chiral heterocyclic sulfur compound selected from each enantiomer of the formula **III** or **IV**



III **IV**

wherein:

n is 1 or 2;

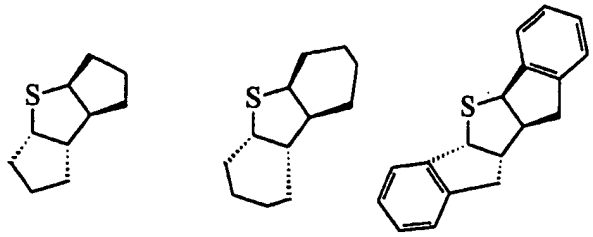
R is selected from alkyl having 1-8 carbon atoms, aryl, and substituted aryl; and

A is selected from a carbocyclic or heterocyclic, aromatic, saturated or partially saturated, mono- or bicyclic ring, which can be further substituted with one or more alkyl or aryl groups, and can comprise one or more additional chiral centers.

8. A compound according to claim 7, wherein R is methyl, ethyl, or isopropyl.

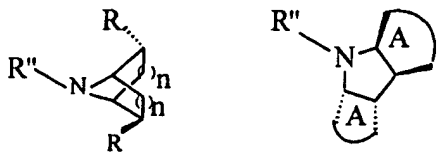
9. A compound according to claim 7, wherein the ring comprises 3 to 8 carbon or heteroatoms per ring.

10. A compound according to claim 9 selected from



11. A chiral heterocyclic sulfur compound according to claim 7 used as an asymmetric catalyst or as a component of an asymmetric catalyst in organic reactions selected from aziridation of aldehydes, epoxidation, thioether-mediation, and other commonly known asymmetric carbon-carbon bond formations.

12. A chiral heterocyclic nitrogen compound selected from each enantiomer of the formula V or VI



V VI

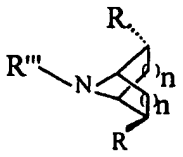
wherein:

n is 1 or 2;

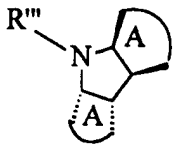
R is selected from alkyl having 1-8 carbon atoms, aryl, and substituted aryl;

A is selected from a carbocyclic or heterocyclic, aromatic, saturated or partially saturated, mono- or bicyclic ring, which can be further substituted with one or more alkyl or aryl groups, and can comprise one or more additional chiral centers;

R″ is selected from hydrogen, alkyl having 1-8 carbon atoms, aryl, substituted aryl, and a group of the formula **VII** or **VIII**



VII



VIII

wherein

the chiral nitrogen heterocycle in the group is identical to the other chiral nitrogen heterocycle in formula **V** or **VI**; and

R‴ is a diradical selected from alkyl diradicals having 1-8 carbon atoms, aryl diradicals, or substituted aryl diradicals.

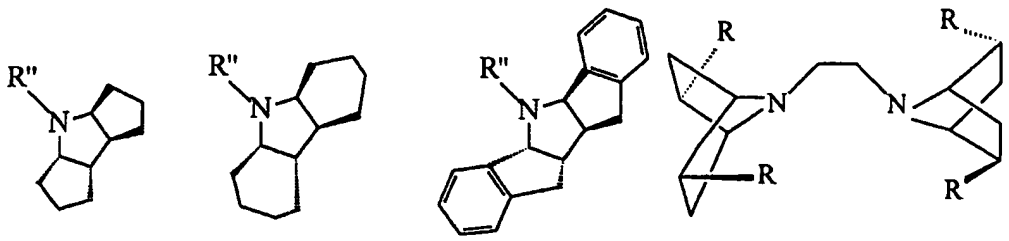
13. A compound according to claim 12, wherein R is methyl, ethyl, or isopropyl.

14. A compound according to claim 13, wherein R″ is methyl.

15. A compound according to claim 12 wherein the ring comprises 3 to 8 carbon or heteroatoms per ring.

16. A compound according to claim 12 wherein the diradical is $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-C_6H_4-$, or ortho-substituted-C_6H_4-.

17. A compound according to claim 12 selected from



18. A chiral heterocyclic nitrogen compound according to claim 12 used as an asymmetric chiral catalyst, a component of an asymmetric catalysis, or a chiral auxiliary in organic reactions selected from Baylis-Hillman, acyl transfer, alkylation, deprotonation, and other commonly known asymmetric carbon-carbon bond formations.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/00146

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :548/418, 427, 452 ; 549/41, 43 ; 568/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/418, 427, 452 ; 549/41, 43 ; 568/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,430,191 A (FORICHER ET AL.) 04 July 1995, col. 1, lines 10-30.	1-6
A	US 5,177,230 A (BURK) 05 January 1993, col. 2, lines 15-30.	1-6
A	US 4,876,361 A (CZOGALLA) 24 October 1989, col. 1, lines 40-65.	7-11
A	US 4,347,254 A (KATSUBE ET AL.) 31 August 1982, col 1, lines 15-20.	7-11
A	US 4,219,657 A (BERGER ET AL.) 26 August 1980, col. 1, lines 10-15.	7-11
A	US 3,803,180 A (BERGER ET AL.) 09 April 1974, col. 1, lines 45-55.	7-11

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 12 MARCH 1998	Date of mailing of the international search report 27 APR 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Y. N. GUPTA Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/00146

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,475,110 A (HUDKINS ET AL.) 12 December 1995, col. 2, lines 5-15.	12-18
A	US 5,137,908 A (FOURIE ET AL.) 11 August 1992, col. 14, lines 5-20.	12-18
A	US 1,911,699 A (LIMPACH ET AL.) 30 May 1933, the entire 1st page.	12-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/00146

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/00146

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07F 9/02 ; C07D 333/50, 333/74, 209/56, 487/00, 209/04, 209/52

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-6, drawn to cyclic phosphine compounds.
Group II, claim(s) 7-11, drawn to cyclic sulfur compounds.
Group III, claim(s) 12-18, drawn to cyclic nitrogen compounds.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions I-III are drawn to structurally dissimilar compounds. They are made and used independently. Cyclic phosphine compounds are not having the same stuctural feature as cyclic nitrogen or cyclic sulfur compounds or vice-versa. These are neither equivalent or suggestive of each other and, thus are not related to each other or relate to a single inventive concept.